

(19) JAPANESE PATENT OFFICE (JP)
(11) Unexamined Patent Application (Kokai) No. HEI 5[1993]-194225
(12) Unexamined Patent Gazette (A)

best ref

(51) Int. Cl.⁵: Classification Symbols: Internal Office Registration Nos.: FI:
A 61 K 31/44 ACL 7252-4C
9/20 B 7329-4C
47/18 J 7433-4C
//(A 61 K 31/44
31:195) 8413-4C

(43) Disclosure Date: August 3, 1993

Request for Examination: Not yet submitted

Number of Claims: 10

(Total pages: 7)

(54) Title of the Invention: Preparation Containing Stabilized Antiulcer Agent

(21) Application No. Hei 4[1992]-322466
(22) Filing Date: November 5, 1992
(31) Claim of Priority Right: Hei 3[1991]-321230
(32) Priority Date: November 11, 1991
(33) Country Claiming Priority: Japan (JP)
(72) Inventor: Naohiro Oishi
Yoshitomi Pharmaceutical Industries Ltd.
Central Research Laboratory
955 Koiwai, O-aza, Yoshitomi-machi,
Chikujo-gun, Fukuoka-ken
(72) Inventor: Toshiyuki Shibata
same address
(72) Inventor: Kuniki Ikeda
same address
(71) Applicant: Yoshitomi Pharmaceutical Industries Ltd. (000006725)
6-9 Hirano-machi 2-chome, Chuo-ku, Osaka-shi, Osaka
(74) Agent Katsu Takamiyashiro, Patent Attorney

SPECIFICATION**(54) [Title of the Invention]**

Preparation Containing Stabilized Antiulcer Agent

(57) [Abstract]

[Constitution] A preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid salt or amino acid alkali salt as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids.

[Effect] It was discovered that benzimidazole compounds have excellent stability and do not discolor when amino acid, amino acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, are blended with benzimidazole compound that is not stable in acid. Preparations containing stabilized antiulcer agent are obtained by using these stabilizers.

[Claims]

[Claim 1] A preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids.

[Claim 2] The preparation according to Claim 1, wherein the benzimidazole compound is 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound.

[Claim 3] The preparation according to Claim 1, wherein the benzimidazole compound is omeprazole, lansoprazole, or 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methylsulfinyl]-1H-benzimidazole sodium salt.

[Claim 4] The preparation according to Claim 1, wherein the amino acid, amino acid acid salt or amino acid alkali salt is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-asparagine, L-asparagine acid sodium salt, L-lysine or L-lysine-L-glutamate, and the buffer is

phosphoric acid alkali metal salt, sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphoric acid, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate or aluminum glycinate.

[Claim 5] The preparation according to Claim 1, which is a tablet, granule or capsule.

[Claim 6] The preparation according to Claim 1, wherein the amino acid, amino acid acid salt or amino acid alkali salt is glycine, glycine hydrochloride, L-alanine, DL-alanine or L-glutamic acid sodium salt, and the buffer is disodium hydrogen phosphate.

[Claim 7] The preparation according to Claim 1, wherein the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, and the buffering agent are blended to produce a core tablet, which is coated with 1-2 layers of undercoating, and an enteric coating is then applied thereupon.

[Claim 8] The preparation according to Claim 1 and Claim 7, wherein acid-controlling substance having a buffering action and, as necessary, buffering agent are contained in the undercoating layer.

[Claim 9] The preparation according to Claim 8, wherein the acid-controlling substance having buffering action in the undercoating layer is magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate or aluminum hydroxide-sodium bicarbonate coprecipitate, and the buffering agent is sodium tartrate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogen phosphate, sodium pyrophosphate, disodium hydrogen phosphate, trisodium phosphate or tripotassium phosphate.

[Claim 10] The preparation according to Claim 1 and Claim 7, wherein the enteric coating is cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetosuccinate, polyvinyl acetate phthalate, carboxymethylethylcellulose or methacrylic acid-acrylic acid copolymer.

[Detailed Description of the Invention]**[0001]**

[Field of industrial utilization] The present invention relates to a preparation containing stabilized antiulcer agent

[Prior art and problems to be solved by the invention] Benzimidazole compounds which have H⁺-K⁺ ATPase inhibition action are useful as digestive ulcer treatments that strongly inhibit stomach acid secretion. This action is strong and persistent, and so these compounds are receiving attention as next-generation digestive ulcer treatments that will supplant histamine H₂ receptor antagonist such as cimetidine. In particular, the benzimidazole compounds described in Japanese Unexamined (Kokai) Patent Application No. Sho 54[1979]-141783, Japanese Unexamined (Kokai) Patent Application No. Sho 61[1986]-60978 and Japanese Unexamined (Kokai) Patent Application No. Hei 1[1989]-6270 have particularly strong stomach acid secretion inhibitory actions, and their clinical effectiveness has been confirmed. However, these benzimidazole compounds have poor stability, and when in solid form, they are unstable with respect to moisture, heat and light. In addition, the substances rapidly decompose and become extremely discolored in acidic to neutral aqueous solutions. With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. When an oral preparation is to be manufactured in this manner using benzimidazole compound, in addition to problems arising from the need for compounding with other components and the use of enteric base coatings, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is necessary to appropriately stabilize these compounds when they are to be formulated in oral dosage forms. A great deal of research has been carried out on stabilizers and stabilization methods for obtaining preparations with stable benzimidazole compounds having antiulcer action; for example, methods that involve blending alkali reaction compounds (Japanese Unexamined (Kokai) Patent Application No. Sho 62[1987]-258320), methods

110-14

that involve the blending of basic inorganic salts of magnesium or calcium (Japanese Unexamined (Kokai) Patent Application No. Sho 62[1987]-277322), and methods that involve the blending of magnesium oxide and mannitol (Japanese Unexamined (Kokai) Patent Application No. Hei 2[1990]-22225).

[0002]

[Means for solving the problems] The inventors of the present invention et al., in light of this state of affairs, carried out painstaking investigations concerning various stabilizers with the objective of stabilizing compositions that contain benzimidazole compounds. The present invention was thus perfected upon the discovery that the above problems can be eliminated by means of using amino acids and buffers in conjunction. Specifically, the present invention relates to a preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound having antiulcer action that is not stable in acids. In the present invention, examples of benzimidazole compounds that have antiulcer action and are not stable in acid include 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds, and specifically, the compounds described in the various aforementioned publications; for example, omeprazole (5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole), lansoprazole (2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole) or 2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium salt.

[0003] In the present invention, examples of amino acids, amino acid acid salts and amino acid alkali salts include glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-asparaginic acid, L-asparaginic acid sodium salt, L-lysine and L-lysine-L-glutamic acid salt. These substances can be used in conjunction, but it is preferable to use glycine, glycine hydrochloride, L-alanine, DL-alanine or L-glutamic acid sodium salt. The term "buffer" refers to an additive that controls the pH in the weakly alkaline range of 8-9. Examples include phosphoric acid alkali metal salts (disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, sodium dihydrogen phosphate and potassium dihydrogen phosphate), sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate,

magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate (product name, Cumulite; Kyowa Chemical Industry Co.) and aluminum glycinate (product name Glycinal; Kyowa Chemical Industry Co.). These substances can be used individually or in conjunction, but disodium hydrogen phosphate is preferred. In addition, the preferred blend amounts of these substances are in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffer with respect to 1 part by weight of benzimidazole compound. However, amounts are not restricted to these ranges. The stabilizer of the present invention can be added together with additives that are commonly used in drugs, for example, mannitol, corn starch, crystalline cellulose and other excipients, hydroxypropylcellulose and other binders, hydroxypropylcellulose with a low degree of substitution, carboxymethylstarch sodium (product name Explotab; Kimura Sangyo), carboxymethylcellulose calcium and other disintegration agents, sodium laurylsulfate, Tween 80 (product name) and other surfactants, and magnesium stearate, talc and other glazes.

[0004] The composition of the present invention is obtained by using a kneader to uniformly blend the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt stabilizer, the buffering agent, the above additives, and water, used as necessary. However, the blending method, for example, can involve blending the benzimidazole compound with the amino acid, amino acid acid salt or amino acid alkali salt and buffering agent to produce a material, which is then blended with the additives. Alternatively, a method can be used wherein the benzimidazole compound is blended with the additives to produce a material to which the stabilizer is added, followed by bringing about uniform contact between the stabilizer and benzimidazole compound. The resulting mixture is then finely granulated with a wet granulator, and the material is then subjected to tabletization to produce uncoated tablets for tablet production. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules.

[0005]

The uncoated or core granules obtained in this manner can be formed into an enteric preparation by coating the core granules with enteric coating. However, in order to eliminate detrimental effects due to the enteric coating base, 1-2 layers of undercoating is applied to the uncoated or core granule. Examples of undercoating bases that can be cited include hydroxypropylmethylcellulose, hydroxypropylcellulose and polyvinylpyrrolidone. Substances that can be added to the undercoating layer include

acid controlling substances having buffering action such as magnesium carbonate, magnéinium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate, aluminum hydroxide-sodium bicarbonate coprecipitate, and as necessary, the aforementioned buffering agents. In addition, examples of enteric coating agents that can be used include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, carboxymethylcellulose and methacrylic acid-acrylic acid copolymer (product name Eudragit). The enteric tablet or granule that is of a dosage form that is appropriate for oral administration can be obtained as described above, and in addition, the granules can be packaged into capsules to produce a capsule. The preparation obtained in this manner experiences little change in external appearance even over long-term storage, and exhibits excellent stability with almost no decrease in content. The preparation of the present invention also has excellent stomach acid secretion inhibition action and antiulcer action, along with low toxicity. As a result, the preparations can be used in the treatment of digestive ulcers in mammals including humans.

[0006]

[Working examples] The present invention is described in additional detail below by providing working examples and application examples, but the present invention is not restricted to these examples.

Working Example 1

100 mg of omeprazole, 100 mg of various amino acids and 100 mg of disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) used as buffering agent were dispersed in 20 mL of water. While maintaining a temperature of 25°C, the change in external appearance over time of the white dispersion was investigated. In addition, the change in external appearance over time at 25°C was observed for a control solution that did not contain either the amino acid or the buffering agent.

[0007]

Table I

		Additive (mg)	Change in appearance, 25°C		
Present Invention	1 day		3 days	7 days	
	Glycine 100 Na ₂ HPO ₄ ·12H ₂ O 100	White	White	White	
	L-Alanine 100 Na ₂ HPO ₄ ·12H ₂ O 100	White	White	Gray-white	
	L-Threonine 100 Na ₂ HPO ₄ ·12H ₂ O 100	White	White	Gray-white	
	L-Isoleucine 100 Na ₂ HPO ₄ ·12H ₂ O 100	White	White	White	
	L-Phenylalanine 100 Na ₂ HPO ₄ ·12H ₂ O 100	White	White	Gray-white	
	None --	Light purple	Purple	Black-purple	
	Amino acid Glycine 100 L-Alanine 100 L-Isoleucine 100	Purple Light purple Light purple	Purple Purple Purple	Black-purple Black-purple Black-purple	
Control	Buffering Agent	Na ₂ HPO ₄ ·12H ₂ O 100	Light brown	Light brown	Light brown
		Sodium polyphosphate 200	Brown tint	Brown tint	Light brown
		Sodium pyrophosphate 200	Brown tint	Brown tint	Light brown
		Sodium tartrate 200	Light purple	Purple	Purple
		Sodium acetate 200	Brown tint	Light purple	Light purple
		Sodium bicarbonate 200	White	Brown tint	Light purple
		Disodium hydrogen phosphate 200	Light brown	Light brown	Light brown
		Magnesium carbonate 200	White	Brown tint	Light brown

[0008]

As a result, it was clear that the use of amino acid and buffering agent in conjunction inhibited omeprazole discoloration better than when either substance was used individually, and that the use of these substances in conjunction stabilized the omeprazole.

[0009]

Working Example 1

In the composition indicated below, the omeprazole, crystalline cellulose, hydroxypropylcellulose with a low degree of substitution, hydroxypropylcellulose and mannitol were introduced into a kneader, and were mixed for about 20 min. A solution produced by dissolving glycine and sodium dihydrogen phosphate (Na₂HPO₄·12H₂O) in an appropriate amount of water was then added to this material, and kneading was

performed. The material was then dried for 30 min at 50°C in a fluidization dryer. After drying, a screen was used to obtain 14-24 mesh granules.

Omeprazole	5.0 mg
Glycine	2.5 mg
Na ₂ HPO ₄ ·12H ₂ O	2.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.5 mg
Total	75.0 mg

[0010] Working Example 2

Granules were obtained from the following composition according to Working Example 1. The L-glutamic acid sodium salt and sodium pyrophosphate were dissolved in purified water and blended.

Omeprazole	5.0 mg
L-glutamic acid sodium salt	2.5 mg
Sodium polyphosphate	1.0 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.0 mg
total	75.0 mg

[0011] Working Example 3

Granules were obtained from the following composition according to Working Example 1. The L-alanine and dipotassium hydrogen phosphate (K_2HPO_4) were dissolved in purified water and blended.

Omeprazole	5.0 mg
L-Alanine	1.5 mg
K_2HPO_4	1.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.5 mg
total	75.0 mg

[0012] Working Example 4

A coating of the following composition was applied to the granules obtained in Working Example 3 to obtain enteric granules. The undercoatings 1 and 2 were applied using a fluidization spray dryer (Okawara) at a feed gas temperature of 75°C and an exhaust gas temperature of 55°C. The enteric coating was applied at a feed gas temperature of 65°C and an exhaust gas temperature of 50°C.

Granules of Working Example 3	75.0 mg
 Undercoating 1	
Hydroxypropylmethylcellulose	3.5 mg
Synthetic hydrotalcite	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)

Total	5.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Sum	13.0 mg
Total	100.0 mg

[0013] Working Example 5

In the following composition, the omeprazole, mannitol, Explotab, sodium laurylsulfate and hydroxypropylcellulose were mixed until uniform, and a solution of L-isoleucine and sodium pyrophosphate dissolved in an appropriate amount of purified water was added thereto. After mixing, the material was dried in a fluidization dryer at 50°C for 30 min. The dried granule powder was then sized with a 24 mesh screen, and magnesium stearate was added. Subsequently, 135 mg tablets (uncoated tablets) were manufactured with a rotary tabletizer.

Omeprazole	20.0 mg
L-isoleucine	3.0 mg
Sodium pyrophosphate	3.0 mg
Mannitol	99.2 mg
Explotab (generic name: carboxymethylstarch sodium)	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

[0014] Working Example 6

A coating of the following composition was applied to the tablets (uncoated tablets) obtained in Working Example 5 to obtain enteric tablets. The undercoatings 1 and 2 were applied using a Hicoater (Freund Co., Ltd.) at a pan rotation rate of 13 rpm, a feed gas temperature of 70°C and an exhaust gas temperature of 40°C. The enteric coating was applied at a feed gas temperature of 55°C and an exhaust gas temperature of 37°C.

Tablet of Working Example 5	135 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.5 mg
Cumulite (generic name: aluminum hydroxide-sodium bicarbonate coprecipitate)	0.4 mg
Purified water	(23.0 mg)
Total	1.9 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg
 Enteric coating	
Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg
Ethanol	(35.0 mg)
Purified water	(10.0 mg)
Sum	3.5 mg
Total	144.5 mg

[0015]

Working Example 7

Core granules having the formulation presented below were manufactured according to Working Example 1. The glycine and sodium pyrophosphate that were used as stabilizers were dissolved in purified water and blended. Cumulite and disodium hydrogen phosphate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) were blended in the undercoating (1) with the objective of preventing blending and modification between the omeprazole in the core grains and the enteric coating. A fluidization spray dryer (Okawara) was used for the film coating. Undercoatings 1 and 2 were applied at a feed gas temperature of 75°C and a exhaust gas temperature of 55°C. The enteric coating was applied at a feed gas temperature of 55°C and an exhaust gas temperature of 40°C.

Core granules

Omeprazole	5.0 mg
Glycine	2.0 mg
Sodium pyrophosphate	2.0 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	52.5 mg
total	70.0 mg

Undercoating 1

Hydroxypropylmethylcellulose	3.2 mg
Cumulite (generic name: aluminum hydroxide- sodium bicarbonate coprecipitate)	1.2 mg
Na ₂ HPO ₄ ·12H ₂ O	0.1 mg
Talc	0.5 mg
Purified water	(60.0 mg)
total	5.0 mg

Undercoating 2

Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	1.0 mg
Talc	0.5 mg

Purified water (65.0 mg)

Total 5.0 mg

Enteric coating

Eudragit L-30D-55 (solid) 15.0 mg

(genetic name: methacrylic acid acrylic acid copolymer)

Polyethylene glycol 6000 1.3 mg

Tween 80 0.7 mg

Talc 3.0 mg

Purified water (50.0 mg)

Sum 20.0 mg

Total 100.0 mg

[0016]

Effect of the invention

Stabilization effects were not obtained when the amino acid, amino acid acid salt or amino acid alkali salt and the buffering agent were used individually and blended in benzimidazole compound. However, it was found that the benzimidazole compound was extremely stable when these substances were used in conjunction. Preparations containing stabilized antiulcer agent were obtained by using these substances in conjunction.